Requirement for deoxycytidine kinase in T and B lymphocyte development.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2010

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PubMed link: 20080663

Funding Grants: Novel Tools and Technologies for Translational PET Imaging of Cell-based Therapies

Public Summary:

Scientific Abstract:
Deoxycytidine kinase (dCK) is a rate-limiting enzyme in deoxyribonucleoside salvage, a metabolic pathway that recycles products of DNA degradation. dCK phosphorylates and therefore activates nucleoside analog prodrugs frequently used in cancer, autoimmunity, and viral infections. In contrast to its well established therapeutic relevance, the biological function of dCK remains enigmatic. Highest levels of dCK expression are found in thymus and bone marrow, indicating a possible role in lymphopoiesis. To test this hypothesis we generated and analyzed dCK knockout (KO) mice. dCK inactivation selectively and profoundly affected T and B cell development. A 90-fold decrease in thymic cellularity was observed in the dCK KO mice relative to wild-type littermates. Lymphocyte numbers in the dCK KO mice were 5- to 13-fold below normal values. The severe impact of dCK inactivation on lymphopoiesis was unexpected given that nucleoside salvage has been thought to play a limited, "fine-tuning" role in regulating deoxyribonucleotide triphosphate pools produced by the de novo pathway. The dCK KO phenotype challenges this view and indicates that, in contrast to the great majority of other somatic cells, normal lymphocyte development critically requires the deoxyribonucleoside salvage pathway.

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